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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,877	12/09/2003	Jill A. O'Loughlin	B0877.70025US00	9392

7590 03/11/2005

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 03/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,877	O'LOUGHLIN ET AL.	
	Examiner	Art Unit	
	Allison M Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-98* is/are pending in the application.

4a) Of the above claim(s) *26-39,49-61,70-85,97 and 98* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-98* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-25, 40-48, 62-69 and 86-96, drawn to an oral delivery composition comprising uricase, creatinase and urease, classified in class 435, subclass 183.

II. Claims 26-39, 83-85 and 97-98, drawn to a method for delivering an oral delivery composition, classified in class 424, subclass 451.

III. Claims 49-50, 70-71 and 81-82, drawn to a method for delivering an oral delivery composition comprising at least one cell, classified in class 424, subclass 93.1.

IV. Claims 51-61, drawn to an oral delivery composition comprising a cell designed to overexpress uricase or creatinase, classified in class 435, subclass 440.

V. Claims 72-80, drawn to an oral delivery composition comprising a cell and urea, classified in class 424, subclass 719.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and IV are distinct inventions and thus are subject to restriction. The inventions are distinct in that the products are not dependent on each other, not to be used together and have different functions, modes of operation, and effects. In the instant case the article of Group IV requires that the article comprises at least one cell that is specifically designed to overexpress at least one of uricase and creatinase; the article of Group I does not require at least one cell to be present in the article, and non of the claims require or describe the uricase or creatinase to be over expressed. For the article of Group IV to require that the composition include at least one cell that overexpresses uricase and/or creatinase makes the article considerably more complicated, as it requires more planning, as consideration must be given to optimal codon usage. The article of Group I that does not require the cells to overexpress uricase or

creatinase could alternatively comprise shuttle vectors that do not express uricase or creatinase at all, much less over express them. Therefore the articles have different compositions, different effects, and different modes of operation and considerably different levels of complexity.

Invention I and V are distinct inventions and thus are subject to restriction. The inventions are distinct in that the products are not dependent on each other, not to be used together and have different functions, modes of operation, and effects. In the instant case the article of Group V requires the composition to comprise at least one cell and additional, un-related chemical compounds such as urea. The article of Group I does not even require a cell to be present in the composition; additionally, there is no requirement for the inclusion of uremic toxins such as urea, uric acid, or creatinine. The inclusion of these unrelated compounds would involve a separate search that would prove burdensome in addition to the already extensive search necessary.

Invention IV and V are distinct inventions and thus are subject to restriction. The inventions are distinct in that the products are not dependent on each other, not to be used together and have different functions, modes of operation, and effects. In the instant case the article of Group IV requires that the article comprises at least one cell that is specifically designed to overexpress at least one of uricase and creatinase; the article of Group V does not require the composition to comprise at least one cell that over expresses uricase or creatinase. For the article of Group IV to require that the composition include at least one cell that overexpresses uricase and/or creatinase makes the article considerably more complicated, as it requires more planning, as consideration must be given to optimal codon usage. The article of Group V that does not require the cells to overexpress uricase or creatinase could alternatively comprise shuttle vectors that do not express uricase or creatinase at all, much less over express them. Additionally, the article of Group V requires the inclusion of un-related chemical compounds such as urea. The article of Group IV does not require the inclusion of uremic toxins such as urea, uric acid, or

creatinine. The inclusion of these unrelated compounds would involve a separate search that would prove burdensome in addition to the already extensive search necessary.

Inventions II and III are distinct inventions and thus are subject to restriction. The inventions are distinct processes in that the methods are not dependent on each other, not to be used together and have different functions, modes of operation, and effects. In the instant case the method of Group III requires the use of an article that comprises at least one cell; the method of Group II does not require any cells to be present in the article to be administered. Additionally, the method of Group II is intended to be administered to patients susceptible to a variety of ailments including gout, end stage renal disease, renal dysfunction, and those patients who have been treated with chemotherapy; the method of Group III is not intended to be administered to patients with any of these susceptibilities or diseases, therefore the methods have different effects.

The articles of Groups I, IV and V are related to the methods of Groups II and III as products and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case any of the articles can be used in either of the methods; therefore, the processes can be practiced with materially different products, and the products can be used in materially different processes of use. The material differences between the individual products and individual methods have been explained above.

Therefore, a search and examination of all inventions in one patent application would result in an undue burden. These inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, different classifications, and a search

for one group does not require a search for another group, restriction for examination purposes as indicated is proper.

During a telephone conversation with Tani Chen on 2/1/05 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-25, 40-48, 62-69 and 86-96. Affirmation of this election must be made by applicant in replying to this Office action. Claims 26-39, 49-61 and 70-85 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, which ever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with

an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in the light of *In re Ochiai, In re Brouwer* and 34 U.S.C § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Status of Application

Claims 1-98 are pending in the current application; claims 1-25, 40-48, 62-69 and 86-96 are being examined for patentability. Claims 26-39, 49-61, 70-85 and 97-98 are withdrawn from consideration.

Information Disclosure Statement

The Prakash et al reference (International Journal of Artificial Organs), reference 14 on the information disclosure statement, was crossed out because it is improperly cited: the year of publication was listed as "1000," where it clearly was meant to be "2000." The examiner has considered the reference and has put the proper citation on the PTO-892.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant fails to provide sufficient written description of acceptable cells besides *E. coli* that can be used in the claimed invention. Applicant specifically points out in the claims and specification that the oral delivery composition is to comprise cells that are not *E. coli*; however, the only working example in the specification uses *E. coli* DH5 cells to produce the claimed article. Applicant fails to suggest alternative cell lines, or disclosure of relevant, identifying characteristics of such suitable cell lines. Therefore, applicant has failed to provide sufficient written description to show the applicant was in possession of the claimed invention. *See Eli Lilly,* 119F. 3d. at 1568, 43 USPQ2d at 1406. See MPEP § 2163.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 1 and its dependents are indefinite because it is not clear by the claim language if the claims are defining the composition of the actual capsule, or the contents which are held within the capsule. For example, it is not clear if the capsule is to be made of isolated uricase, creatininase, urease, cells comprising uricase, creatininase, urease, alginate, an enteric coating and/or a pharmaceutically acceptable carrier or if the capsule is to hold the enzymes, cells that comprise the named enzymes, alginate an, enteric coating and/or a pharmaceutically acceptable carrier. Applicant uses the same term, "comprising," to describe what appears to be the composition of the actual capsule shell, such as the enteric coating and alginate, as well as what appears to be contained within the capsule shell, such as the enzymes and cells. Applicant needs to clearly differentiate the composition *of* the capsule from the composition contained *within* the capsule.

Furthermore, claims 6 and 8 use the term broad term "substantially" without providing adequate limitations or guidelines in the specification to properly define what is being considered to be a "substantial" amount. With no numerical values or limits described in the claims one of ordinary skill in the art cannot determine what applicant is considering a "substantial" amount to be released or impeded.

Additionally, claim 8 uses the term "therethrough" without providing adequate antecedent basis, as it is not clear what the "therethrough" is referring to. It appears applicant intends to refer to the transport of urea, uric acid and creatinine through the capsule; it would be remedial to claim, "...of at least one of urea, uric acid, and creatinine through the capsule."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Marquisee (US Patent 3,954,678).

Marquisee teaches a semipermeable microcapsule which comprises silica gel within a semipermeable membrane. The capsule can contain a biological catalyst, preferably urease or urate oxidase (uricase) (See col. 2, ln 38-57) (Claim 1). The membrane is impermeable to these enzymes, therefore the enzymes cannot be released externally of the capsule (See col. 2, ln 29-37) (Claim 6). Additional auxiliary cell stabilizing agents can be added to the silica gel to allow for normal separation and purification of the microcapsule without cell collapse, such agents can include alginate (See col. 2, ln 1-10) (Claim 7). Though Marquisee does not specifically teach the semipermeable microcapsules to be used for oral delivery, the oral delivery composition as claimed is the same as that taught in the prior art, therefore the semipermeable microcapsule of Marquisee is considered one and the same as the oral delivery composition as in the current application; therefore the reference anticipates the subject matter.

Claims 86-88, 92 and 93 rejected under 35 U.S.C. 102(b) as being anticipated by Wolfe et al (The International Journal of Artificial Organs, 1987).

Wolfe et al teach an oral delivery composition comprising microencapsulated urease enzymes and zirconium phosphate (See Pg. 267). The zirconium phosphate works as an ammonium ion sorbent (which applicant calls an ammonium uptake species) (Claim 92). Wolfe et al use 2 mg of isolated urease, therefore multiple enzymes, at least three urease enzymes, were used in each capsule (Claims 86-88). The microcapsules are intended for oral delivery, therefore they are contained within a pharmaceutically acceptable carrier (Claim 93). Because applicant does not require the at least two, or at least three, isolated uremic enzymes to be different isolated uremic enzymes, Wolfe et al anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-8, 10-17, 25, 40-45, 47-48, 52-66, 68-69, 86-91 and 93-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (US Patent 6,217,859), in view of Setala (US Patent 4,022,883), and further in view of Yamamoto et al (US Patent 5,627,065) and Shigyo et al (US Patent 5,728,562) and in light of The Online Medical Dictionary.

Chang et al teach an article comprising an oral delivery composition, comprising a microencapsulated genetically engineered microorganism in a pharmaceutically acceptable carrier (which applicant calls a capsule comprising at least one cell transfected with a gene) (See Chang et al, col. 2, ln 24-31). The microencapsulating material can be an alginate-polylysine-alginate (See col. 2, ln 38-45). The microencapsulating material is able to entrap the microorganisms so that the microorganisms are not released externally from the capsule, but does not impede mass transport of the undesirable molecules for removal to enter in contact with the entrapped microorganisms (See col. 2, ln 46-52). In a preferred embodiment Chang et al teach encapsulating genetically engineered *E.coli* DH5 cells, which are transfected with the urease gene from *Klebsiella aerogens*, for the purpose of urea removal (See col. 3, ln 58- col. 4, ln 40 & Claim 9).

Though Chang et al only teach transfecting a cell with the urease gene, for the purpose of urea removal in uremic patients, it would have been obvious to one of ordinary skill in the art at the time the invention was made to additionally transfect the cell with the uricase and creatininase genes in addition to the urease gene. One of ordinary skill in the art would have been motivated to use cells transfected with uricase, creatininase and urease genes so the cell would produce uricase, creatininase and urease. Uric

acid, creatine and urea are all uremic toxins that accumulate in uremic patients (See Setala, col. 3, ln 18-36). Uricase, creatininase and urease break down uric acid, creatine and urea, respectively, to more dilute compounds which can be excreted in the urine (See The Online Medical Dictionary "Uricase," "Allantoin," "Creatininase," "Creatinine" and "Urea"). Therefore, one of ordinary skill in the art would have been motivated to use a cell transfected with uricase, creatininase and urease, encapsulated in the microcapsule taught by Chang et al, in order to aide in the breakdown and removal of three uremic toxins that accumulate in uremic patients. One would have expected success transfecting a cell with the uricase gene because Shigyo et al teach isolation of the uricase gene from Bacillus sp. and subsequent transfection into and expression in *E.coli* cells (See Shigyo et al, col. 6, ln 15- col. 8, ln 34). One would have expected success transfecting a cell with the creatininase (creatinine amidohydrolase) gene because Yamamoto et al teach isolation of the creatininase gene from *Pseudomonas putida* PS-7 and subsequent transfection into and expression in *E.coli* cells (See Yamamoto et al, col. 3, ln 6-57 & Claim 5). One would have expected the transfected cells encapsulated in the microcapsule of Chang et al to successfully secrete all three enzymes because Chang et al teach a genetically engineered cell, transfected with urease, successfully secreted the urease enzyme in levels that were sufficient to lower urea levels in uremic patients (See col. 8, ln. 38- col.9, ln 5). Uricase and creatininase are known to break down uric acid and creatine, respectively, therefore one of ordinary skill in the art would expect similar success removing uric acid and creatine when uricase and creatininase are delivered to the gastrointestinal tract of a uremic patient (Claim 40, 42, 44-45 and 47). Therefore the microencapsulated cell of Chang et al is an effective delivery device capable of delivering all three gene product enzymes to remove the three uremic toxins.

Alternatively, it would have been obvious to one of ordinary skill in the art to encapsulate multiple cells using the method of Chang et al, wherein a first cell is transfected with only urease, a second cell is transfected with only creatininase, and a third cell is transfected with only uricase (Claims 41 and 43). Still further, multiple cells could be transfected with the three genes in any combination of

ways, wherein a first cell is transfected with two of the genes of interest, and a third cell is transfected with only the remaining third gene of interest. Any order and combination of genes transfected into a single cell or multiple cells would be obvious to one of ordinary skill in the art, as long as all three genes were present within the microcapsule taught by Chang et al because Chang et al does encapsulate multiple cells (See col.4, ln 41-64). One of ordinary skill in the art would have been motivated to manipulate the order and combination of genes transfected into single or multiple cells based on the availability of transformed cells, if purchased commercially, or if made in the laboratory, based on the transfection vectors used, as some vectors may contain two of the genes, allowing them to be activated by a single promoter, while a third gene may be contained on a separate vector that is induced by a separate promoter. The combination of the genes of interests in a single or in multiple cells would be an obvious choice of experimental design. The order and combination of the genes encoding the enzymes, whether they be in a single or multiple cells, will not effect the efficiency of the article, as all genes will be expressed, and therefore all three enzymes will be present in the microcapsule; therefore one would expect equal levels of success no matter what order or combination the genes are transfected in the cells.

Still further, though Chang et al, Shigyo et al and Yamamoto et al teach examples wherein the urease, uricase and creatininase genes were transfected into *E.coli* cells, respectively, it would have been obvious to one of ordinary skill in the art to use any suitable microorganism as the host cell in which to transfect the three genes of interest (Claims 64-66 and 68). The choice of host microorganism would have been a matter of experimental design choice; any suitable, biocompatible bacteria that can easily be genetically engineered would have been suitable. One of ordinary skill in the art would have been motivated to use any suitable microorganism because Chang et al teach that any suitable microorganism can be used in accordance with their invention, including, for example, *Bacillus pastteuri* (See Chang et al col. 3, ln 58-65). One would have expected success because one of ordinary skill in the art would be able to select a microorganism suitable for transfection and in vivo use, as methods of transfection are

well known in the art (See, e.g. Shigyo et al and Yamamoto et al), and Chang et al teach a general method of encapsulation that is applicable to multiple cell types.

Alternatively, instead of encapsulating the entire genetically engineered cell, as in the method of Chang et al, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the oral delivery composition of Chang et al to comprise a microcapsule comprising isolated urease, uricase and creatinase, instead of cells transfected with the genes for urease, uricase and creatinase, as described above (Claims 1-4, 6-8, 25, 86-91 and 93). One of ordinary skill in the art would have been motivated to encapsulate isolated enzymes, instead of whole cells, because isolated enzymes can be easily purchased from commercial sources, are less complicated in terms of biocompatibility, immune reactions and overall safety than genetically modified organisms, isolated enzymes require less effort in storage, packaging and transportation, and compositions comprising isolated enzymes are easier to get approved by the FDA than genetically modified organisms. One would have expected success because isolated urease, creatininase and uricase enzymes would have the same effect on breaking down urea, creatine and uric acid, respectively, as enzymes produced by cells transfected with the same genes since the active product is the same; therefore would one would have expected the same level of success as was obtained using transfected cells, as taught above. Furthermore, because isolated urease, creatininase and uricase encapsulated in the microcapsule of Chang et al would have the same effect as the enzymes encoded for by the encapsulated transfected cells, it would further have been obvious to encapsulate both cells (either *E.coli* or any other suitable microorganism, see teachings above) transfected with the genes for urease, creatininase and uricase, and isolated urease, creatininase and uricase because combining two compositions that have the same effect to create a third composition with the same effect as the first two, is prima facie obvious. See *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). The combination of isolated enzymes and enzymes encoded for by transfected cells would

only strengthen the degradation of the uremic toxins in the uremic patient's system (Claims 10-17, 48, 69 and 94-96).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 5 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (US Patent 6,217,859), in view of Setala (US Patent 4,022,883), further in view of Yamamoto et al (US Patent 5,627,065) and Shigyo et al (US Patent 5,728,562), and still further in light of The Online Medical Dictionary and Merriam-Webster Online Dictionary.

Chang et al teach an article comprising an oral delivery composition, comprising a microencapsulated genetically engineered microorganism in a pharmaceutically acceptable carrier (which applicant calls a capsule comprising at least one cell transfected with a gene) (See Chang et al, col. 2, ln 24-31). In a preferred embodiment Chang et al teach encapsulating genetically engineered *E.coli* DH5 cells, which are transfected with the urease gene from *Klebsiella aerogens*, for the purpose of urea removal (See col. 3, ln 58- col. 4, ln 40 & Claim 9).

It would have been obvious for the oral delivery composition of Chang et al to comprise a microcapsule comprising isolated urease, uricase and creatinase, as taught above.

Though Chang et al is silent on the presence of an enteric coating on the microcapsules, as well as the microcapsules resistance to acid degradation, it would have been obvious to one of ordinary skill in the art at the time the invention was made to enterically coat the modified capsule of Chang et al (modified to comprise isolated urease, uricase and creatininase), in order to protect the capsule from acid degradation in the stomach so that it may pass, unaltered, into the intestines where it will function to degrade the uremic toxins. By definition, an enteric coating is designed to pass through the stomach, unaffected by the gastric juices and acids, to disintegrate in the intestines (See Merriam-Webster Online

Dictionary). Chang et al do state that the microcapsules are to function in the intestines (See col. 3, ln 26-39); therefore one of ordinary skill in the art would have been motivated to enterically coat the microcapsules to protect them from acid degradation in the stomach, allowing unaltered passage to the intestines, where they will act to degrade the uremic toxins (Claims 5 and 9). One would have expected success because enteric coating of capsules and other medicinal preparations for the purpose of protection from acid degradation is well known to one of ordinary skill in the art. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 18-21, 46, 67 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (US Patent 6,217,859), in view of Setala (US Patent 4,022,883), further in view of Yamamoto et al (US Patent 5,627,065) and Shigyo et al (US Patent 5,728,562), and still further in view of Sparks et al (Trans. Am. Soc. Artif. Intern. Org, 1972) and Wolfe et al (The International Journal of Artificial Organs, 1987), and in light of The Online Medical Dictionary.

Chang et al teach an article comprising an oral delivery composition, comprising a microencapsulated genetically engineered microorganism in a pharmaceutically acceptable carrier (which applicant calls a capsule comprising at least one cell transfected with a gene) (See Chang et al, col. 2, ln 24-31). In a preferred embodiment Chang et al teach encapsulating genetically engineered *E.coli* DH5 cells, which are transfected with the urease gene from *Klebsiella aerogens*, for the purpose of urea removal (See col. 3, ln 58- col. 4, ln 40 & Claim 9).

It would have been obvious for the oral delivery composition of Chang et al to comprise a cell that is additionally transfected with the uricase and creatininase genes in addition to the urease gene, as taught above. Though Chang et al uses an *E.coli* cell, it would have been obvious to use a cell that is not *E. coli*, as taught above. Additionally, it would have been obvious for the oral delivery composition of

Chang et al to comprise a microcapsule comprising isolated urease, uricase and creatinase, thus the cell would contain at least two isolated uremic enzymes, as taught above.

Chang et al does not teach including an ammonium uptake species in the capsule; however, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include an ammonium uptake species in the capsules. Such ammonium uptake species include zirconium phosphate (See Kominami et al, col. 5, ln 51-66 & Wolfe et al, Pg. 269), activated carbon (See Kominami et al, col. 5, ln 51-66) and oxidized starch (which applicant calls oxystarch) (See Sparks et al, Pg. 459) (Claims 18-21, 46, 67 and 92). Kominami et al, Wolfe et al and Sparks et al have all shown zirconium phosphate, activated carbon and oxidized starch to be suitable sorbents for the adsorption of ammonia, which is formed by the breakdown of urea by urease (See The Online Medical Dictionary, "Urease"). Therefore one of ordinary skill in the art would have been motivated to include at least one of zirconium phosphate, activated carbon and oxidized starch in the modified microcapsules of Chang et al in order to adsorb the excess ammonia created by the breakdown of urea. One would have expected success because zirconium phosphate, activated carbon and oxidized starch are all taught to adsorb ammonia (See Kominami et al, Wolfe et al and Sparks et al). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 22-24, 46, 67 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (US Patent 6,217,859), in view of Setala (US Patent 4,022,883), further in view of Yamamoto et al (US Patent 5,627,065) and Shigyo et al (US Patent 5,728,562), and still further in view of Smith et al (US Patent 4,857,555) and in light of The Online Medical Dictionary.

Chang et al teach an article comprising an oral delivery composition, comprising a microencapsulated genetically engineered microorganism in a pharmaceutically acceptable carrier (which applicant calls a capsule comprising at least one cell transfected with a gene) (See Chang et al, col. 2, ln

24-31). In a preferred embodiment Chang et al teach encapsulating genetically engineered *E.coli* DH5 cells, which are transfected with the urease gene from *Klebsiella aerogens*, for the purpose of urea removal (See col. 3, ln 58- col. 4, ln 40 & Claim 9).

It would have been obvious for the oral delivery composition of Chang et al to comprise a microcapsule comprising isolated urease, uricase and creatinase, as taught above.

Chang et al does not teach including an ammonium uptake species in the capsule; however, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include an ammonium uptake species in the capsules, such as glutamine synthetase (which applicant calls an ammonium uptake species). Smith et al teach that glutamine synthetase is responsible for catalyzing the synthesis of glutamine from glutamate and ammonia (See Smith et al, col. 1, ln 34-50); the glutamine produced by this reaction is readily used by the body in a variety of natural ways. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include glutamine synthetase in the modified microcapsule of Chang et al (Claims 22-24, 46, 67 and 92). One would have been motivated to include glutamine synthetase in the modified microcapsule of Chang et al in order to naturally utilize the excess ammonia produced by the break down of urease to synthesize glutamine, a naturally occurring amino acid that aides the body naturally. One would have expected success because Smith et al teach that glutamine synthetase catalyzes the reaction of glutamate and ammonia to form glutamine, which can then forth be utilized directly in the gastrointestinal tract as respiratory fuel (See Smith et al, col. 1, ln 34-col. 2, ln 2). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M Ford whose telephone number is 571-272-2936. The examiner can normally be reached on M-F 7:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER